UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	**June 7, 2004**
LISZIEWICZ, et al.	:	**Atty Docket No. RGT 9771**
DIVISION OF **Serial No. 09/153,198**	:	**Group 1632**
Filed: 15 September 1998	:	**Examiner: Wilson**

For: Method of Delivering Genes into Antigen Presenting Cells of the Skin

Mail Stop – No Fee Amendment
Commissioner of Patents
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INTRODUCTORY COMMENTS[1]

In response to the Office action bearing a mail date of March 10, 2004, please enter the enclosed amendments and remarks of record. Claims 23-33, 35, and 37-42 are currently under consideration. Claims 34 and 36 have been cancelled. Claims 23, 25, 27-30, 32, 33, 35 and 37 are currently amended as suggested by the Examiner and Claim 42 is added. Claim 42 finds support at least at Col. 15, lines 38-39 of the parent patent. The Claims have been amended for the purpose of expediting prosecution. The Specification has been amended to update the status of patent applications. The amendment filed 2-21-02 is not objectionable as introducing new matter to the disclosure of the invention. The sentence added to the paragraph on page 13, line 26, is quoted at least from original Claim 7 of the parent application.

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[1] This paper is being forwarded by fax to Mail Stop – No Fee Amendment, Commissioner of Patents, P.O. Box 1450 Alexandria, VA 22313-1450 in care of the referenced Examiner on June 7, 2004. Signed Valerie E. Looper Valerie E. Looper (410) 715-5771

AMENDMENTS TO THE CLAIMS

Please amend the Claims as follows.

Claims 1-22 (cancelled)

23. (Amended) A method of ~~transducing~~ transfecting ~~antigen-presenting~~ antigen presenting cells ~~of the skin~~, the steps comprising

selecting a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives, and mixtures thereof,

and applying the complex to the skin or mucosa surfaces of an animal,

wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, wherein the immunogenic protein is from a lentivirus.

24. The method of Claim 23, wherein the compound is selected from the group consisting of glucose and polyethylenimine derivatives.

25. (Amended) The method of Claim 24, wherein the polyethyleninine derivative targets a ~~the mannose~~ receptor found on the surface of antigen presenting cells.

26. The method of Claim 25, wherein the derivative is mannosylated polyetheylenimine.

27. (Amended) The method of Claim 26, wherein the mannosylated polyethylenimine is ~~derived~~ from a ~~linear~~ PEI 22 kDA a.

28. (Amended) The method of Claim 23, wherein the complex is electrostatically neutral. ~~(page 25, lines 9-32).~~

29. (Amended) The method of Claim 23, wherein the complex comprises ~~about~~ 3:1-10:1 molar equivalent of either polyethylenimine or polyethylenimine derivative amine per molar equivalent of DNA phosphate ~~ratio~~. ~~(page 25, lines 26-27, page 24).~~

(Amended)

30. The method of Claim 29, wherein the complex comprises ~~about~~ 5:1 molar equivalent of ~~polyethylenimine or~~ polyethylenimine derivative amine per molar equivalent of DNA phosphate ~~ratio~~. ~~(page 25, lines 26-27, page 24).~~

31. The method of Claim 23, wherein the gene delivery complex is formulated in a glucose solution.

32. (Amended) The method of Claim 31, wherein the glucose solution is ~~about~~ 5-10% glucose.

33. (Amended) The method of Claim 32, wherein the glucose solution is ~~about~~ 8% glucose.

34. (Cancelled)

35. (Amended) The method of Claim ~~34~~23, ~~wherein the activating step is performed by~~ further comprising one or more steps from the group consisting of receptor stimulation, toxin activation, or tissue or cell injury.

36. (Cancelled)

37. (Amended) The method of Claim ~~36~~23, wherein the ~~reverse transcriptase dependent virus~~ lentivirus is a human immunodeficiency virus.

38. The method of Claim 37, wherein the human immunodeficiency virus is replication-defective.

39. The method of Claim 38, wherein the human immunodeficiency virus is integration-defective.

40. The method of Claim 23, wherein the DNA is a plasmid.

41. The method of Claim 23, wherein the cells are Langerhans cells.

42. (New) The method of Claim 29, wherein the complex comprises 3:1 molar equivalent of polyethylenimine amine per molar equivalent of DNA phosphate.

AMENDMENTS TO THE SPECIFICATION

At page 2, line 3
Related Application Information

This application is a division of USPN 6,420,176, which is a continuation-in-part of USSN 60/058,933, filed September 15, 1997, both of which are incorporated herein as if set forth in full.

At page 17, line 29

Drug combinations that are effective to at least temporarily inhibit HIV replication are known. The inventors have shown that drug combinations including hydroxyurea, one or more reverse transcriptase inhibitors and, optionally, one or more protease inhibitors are particularly effective, and, for some patients, allow the possibility of stopping drug treatment for extended periods of time. See USSN 09/056,691, filed Apr. 8, 1998, U.S. Patent No. 5,977,086, "Method of Inhibiting HIV by Combined Use of Hydroxyurea, a Nucleoside Analog, and a Protease Inhibitor, USSN 09/048,886 filed Mar. 26, 1998, U.S. Patent No. 6,251,874 Method of Inhibiting HIV using Hydroxyurea and Reverse Transcriptase Inhibitor *in vivo* and USSN 09/048,576, filed March 26, 1998, Method of Rendering a HIV Population Replication Incompetent *in vivo*, (abn) all of which are incorporated herein by reference as if set forth in full. The present invention includes the treatment of a patient with active HIV infection with an appropriate drug combination until the viral load in the blood has reached a suitably low level, less than about 50,000 copies per ml, preferably less than 10,000 copies per ml, more preferably less than 200-500 copies per ml. The patient is then vaccinated using the present invention while the drug combination suppresses replication of the wild-type virus.

REMARKS

It is believed the Examiner's concerns have been fairly met by the amendments above and remarks below. Favorable consideration is solicited.

Rejections under 35 USC § 112, 1st para
Claims 23-41

Claims 23-41 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner states that the genus of antigen presenting cells (APCs) in claim 23 is new matter. The Examiner states that the specification as originally filed did not contemplate transducing any APCs other than dendritic cells.

The Examiner states that the phrase "mixtures thereof' (claim 23) is considered new matter. The Examiner states that the specification does not contemplate combining PEI with derivatives of PEI or combining different derivatives of PEI. The Examiner admits that claim 8 as originally filed stated "wherein the complex is selected from the group consisting of DNA conjugates of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof"; however, the claim was rejected under indefiniteness because it could not be determined what the phrase meant (see first office action in parent application). However, the Examiner states that the phrase still constitutes new matter because of the indefiniteness of the claim as originally filed, that it is not readily apparent that the phrase was intended to encompass mixing PEI with PEI derivatives or mixing different PEI derivatives as encompassed by the claims as amended, and that therefore, the specification as originally filed did not support mixing PEI with PEI derivatives or different PEI derivatives.

Claim 23 has been rejected under new matter, allegedly because no support for the limitations in the claim has been provided. For example, the Examiner states that "transducing APCs of the skin" in any "animal" by applying the complex to the "skin or mucosa surfaces" of the animal cannot be found in the specification as originally filed.

Claim 25 has been rejected under new matter because the specification as originally filed did not complete the genus of polyethylenimine derivates that target the mannose receptor. The Examiner takes the position that only such PEI described in the specification that targets the mannose receptor is mannosylated PEI as in claim 26, which is not adequate representation of the genus.

The Examiner states that support for a mannosylated PEI "derived from a linear PEI 22 kDA in claim 27 cannot be found in the specification as originally filed.

The Examiner states that support for "electrostatically neutral" in claim 28 cannot be found on pg 25, lines 26-27 or pg 24.

The Examiner states that the phrase "about 3-10:1 molar equivalents" (claim 29) or "about 5:1 molar equivalents" (claim 30) is new matter. The Examiner takes the position that support for the limitations of claims 29 and 30 cannot be found on pg 25, lines 26-27 and pg 24, and admits that page 22, lines 9-16, teaches that at the 5:1 (N: P) ratio, PEI-man-DNA is neutral. The Examiner states further that the specification states that N and P stand for nitrogen and phosphorus; however, the specification does not state that the N must be from polyethylenimine and the P must be from the DNA as claimed. Nor, according to the Examiner, does the specification distinguish that molar equivalents and not the number of nitrogen and phosphorus determine the 5:1 ratio, nor does the specification contemplate the molar ratio is "about 5". Therefore, the phrases are new matter.

The Examiner admits that the phrase "glucose solution" in claim 31 is found on pg 22, lines 35-36.

The Examiner says the phrase "about 5-10" (claim 32) and "about 8" (claim 33) are new matter. The specification on page 22, lines 33-36, state that DNA was mixed in 100 mM PEIman in a 5-10% glucose solution (optimum 8%). The Examiner contends that the specification does not contemplate expanding the range of 5-10% or 8% to about 5-10% or 8%. Therefore, according to the Examiner, the use of "about" with 5-10% or 8% was not contemplated in the specification as originally filed.

The Examiner says that support for the limitation of activating the APCs of the skin or mucosa in claim 34 cannot be found and is new matter.

The Examiner says that support for the limitation of activating the APCs of the skin or mucosa by receptor stimulation, toxin activation, or tissue or cell injury in claim 35 cannot be found and is new matter.

The Examiner says that support for proteins "derived" from a reverse-transcriptase dependent virus in claim 36 cannot be found and is new matter. The Examiner states that the term "derived" is not in the specification as originally filed in context of proteins isolated from viruses; that the genus of RT-dependent viruses was not contemplated in the specification as originally filed, and that the species of HIV as in claim 37 does not represent the genus.

Response – Claims 23-34

In response the Applicants point to specific disclosure that supports the Claims as written. This case is a division of USPN 6,420,176. No new matter has been added to this case. Because the Examiner has lodged new matter rejections, except where noted, reference is made to the printed copy of the parent patent.

The term "antigen presenting cells" appears at least in the title and abstract of the parent patent, USPN 6,420,176, and therefore cannot constitute new matter.

The term "mixtures thereof" as found in Claim 23 is admittedly found in claim 8 as originally filed. The Examiner quotes original Claim 8 as including the following language: "wherein the complex is selected from the group consisting of DNA conjugates of sugars, polyethylenimine, polyethylenimine derivatives, and mixtures thereof." That ends the enquiry. The phrase is not new matter. The Examiner's comment, that Claim 8 was originally rejected for indefiniteness, does not convert the claim language to new matter. Further, the Applicants point out that the Examples in the parent patent include a variety of combinations, including DNA and glucose, DNA and PEI (in glucose solution), DNA and PEI-mannose, -galactose, -glucose (in glucose solution), which represent several classes of the claimed mixtures. See particularly Examples 6, 7 and 10.

Claim 23 is not objectionable as containing new matter because it is, as the applicant previously pointed out, supported by the text of the parent patent and claims as originally filed. As discussed above, the phrase "antigen presenting cells" is not new. To the extent the objection is directed to the phrase "of the skin, " it is noted that the title to the patent was originally amended to conform to the title bestowed on the corresponding PCT

application under PCT Rule 4.3. The Applicants were notified of this change in the PCT International Search Report. This action by the ISA/US is objective evidence that the phrase is not new matter. Original Claim 17 supports the term "animal;" Original Claim 19 includes the language "skin or mucosa surfaces" which is also found in the parent patent at least at Col. 11, lines 50-51: "The complex can be applied on the skin or mucosa surfaces directly." The patent includes Examples 8 ("In Vivo Gene Delivery to Skin Langerhans Cells") which concludes that "Therefore, the sugar modified gene delivery system is preferred to transduce antigen presenting cells." See Col. 16, lines 37-38. The cited phrases in Claim 23 are not objectionable as new matter.

The language "polyethyleneimine derivative" of Claim 25 is admittedly found in original Claim 8, and therefore is not objectionable as new matter. Further, to the extent this objection is based on the position that PEI-mannose was the only material used that targets the mannose receptor, the Applicants point out that the patent includes Example 6, "Specifically Targeting DC via Mannose Receptor" where PEI modified with different sugars was chosen to target the mannose receptor....(Col. 14, lines 52-53). Table 1 of that example includes results of various PEI derivatives, including PEI-mannose, -galactose, and -glucose. Col. 15, line1.

The term "linear PEI 22K Da derivatized mannopentose" is found in the parent patent at Col. 10, line 41.

The term "electrostatically neutral" is found at Col. 15, lines 28-29, and an extended discussion as to how this trait is utilized in the invention is found at Col. 15, lines 34-57. The neutral complex of PEI-mannose-DNA is disclosed to be more efficient than the neutralized complex of PEI-DNA at Col. 15, lines 52-57.

The phrase "about 3-10:1 molar equivalents" (claim 29) or "about 5:1 molar equivalents" (Claim 30) is not new matter. Support for the limitations is found in the parent patent at Col. 15, lines 34 to 44. The parenthetical phrase found at Col. 15, lines 39-44 explains the presence of the word "molar."

The term "about" in Claims 32 and 33 are not new matter. These ranges are described in the specification as part of actual experiments that were performed and which worked. The clear implication is that these ranges are not critical. Under the circumstances, the use of the word "about" is entirely consistent with the disclosure, and is not new matter.

Support for the limitation of activating the APCs of the skin or mucosa is found in the parent application at Col. 11, lines 50-55: "The complex can be applied on the skin or mucosa surfaces directly....Activation may be achieved by receptor stimulation (e.g., mannose receptor), toxin activation (cholera toxin), a tissue or cell injury....)

With respect to the objection to "derived" the applicants note this objection is inapplicable to the claims as amended because the term has been deleted.

Rejections under 35 USC § 112, 1st para

Claims 23-41

Claims 23-41 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The Examiner states that the claims are drawn to transducing antigen presenting cells (APCs) of the skin by applying a complex to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding a an immunogenic protein and ii) sugar, polyethylenimine (PEI), a PEI derivative, or mixture thereof.

The Examiner says the specification suggests using the method claimed to induce an immune response in a mammal (pg 20, Example 4) but states without citation that merely inducing an immune response in a mammal, in and of itself, does not have a use by itself because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, the Examiner takes the position that inducing an immune response according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. The Examiner adds that the methods using DNA encoding an immunogenic protein as claimed lack written description because the specification does not provide adequately describe how to induce a therapeutic or prophylactic immune response using the method claimed.

The Examiner states that the genus of antigen presenting cells (APCs) in claim 23 lacks written description, and states that the specification as originally filed did not contemplate transducing any APCs other than dendritic cells. The Examiner states that the species of dendritic cells is not adequate to support the genus of APCs.

The Examiner states that Claims 36-39 require using DNA encoding a protein derived from a reverse transcriptase dependent virus. The Examiner states that the Applicants describe using plasmids encoding replication-defective, integrase-defective retroviruses in the method claimed which are described in related application 08/989,301 as non-lethal and capable of inducing a therapeutic/prophylactic immune response. However, the Examiner points to an earlier reference cited Adachi (J. Virol., Aug. 1986, Vol. 59, pg 284-291) taught such viruses were still infectious. "Replication defective retroviruses" that are non-lethal and capable of inducing a therapeutic/prophylactic immune response are not adequately described by applicants. Nowhere have applicants provided any evidence that the amount of expression of viral protein is adequate to induce a therapeutic/prophylactic immune response or that the virus does not replicate too much and cause disease. Use of the plasmids encoding replication-defective retrovirus in animals as claimed would not treat or prevent disease because the virus would replicate and cause disease. Applicants appear to be attempting to find a retrovirus that expresses adequate viral antigen such that a cellular immune response can be obtained, wherein said retrovirus replicates to a low degree without causing disease. Naming a type of material that may exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method of using replication-defective retroviruses without defining what means will induce a therapeutic/prophylactic effect without causing infection is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived.

(See Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)).

The phrase "PEI, PEI derivatives and mixtures thereof' in claim 23 lacks written description. The specification does not contemplate combining PEI with derivatives of PEI or combining different derivatives of PEI. It is not readily apparent that applicants were in possession or even contemplated any "mixture thereof' as broadly claimed.

Response – Claims 23-41

The present rejection contains errors of law and fact that affect the analysis of the patentability of the Claims. It is the *claimed* invention that must be analyzed. As discussed in more detail below, the claimed invention relates to a method of transducing antigen presenting cells. The application contains experiments that demonstrate how to achieve this specific result. No further showing of utility, such as therapeutic or prophylactic effect, is required, as a matter of law. See In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436 (Fed. Cir. 1995) (finding that antitumor activity in vitro meets the utility requirement under the patent laws and explaining that the PTO must not confuse its role with that of the FDA, which does require proof of therapeutic or prophylactic effect). However, the Applicants point out that a Declaration by one of the inventors filed on or about April 30, 2001 in the parent case, USPN 6,420,176, includes animal data showing that the immune responses disclosed in the parent patent were associated with a therapeutic effect – animals that already were exhibiting signs of AIDS, and who were beginning to fail on the state-of-the-art drug treatment were treated with the claimed complex and subsequently exhibited control of virus replication as well as significantly improved survival time.

The Present Invention

The present invention relates to a method of transfecting antigen presenting cells, the steps comprising selecting a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, wherein the immunogenic protein is from a lentivirus.

Antigen presenting cells

As discussed above, the phrase "antigen presenting cells" finds support in the specification at least in the title, abstract of the parent patent, as well as original claim 1 of the parent application, together with the Summary of the Invention (Col. 5, lines 41-43: "A further object of this invention is to provide an improved method of genetic immunization

by increasing the efficiency of gene transfer to antigen presenting cells." At Col. 7, line 47, under the heading "Target Cells, the application discloses that

> This invention can be used with any cells capable of receptor-mediated endocytosis or phagocytosis. That target cells must express a receptor site which, upon binding with a complementary molecule, can bring the desired molecule into the endosome or phagosome. For the inventor's present purpose, such cells are preferably cells which participate in the immune response. They include cells which can engage in receptor-mediated endocytosis and phagocytosis of antigens. Such cells include, for example, B-cells, mononuclear phagocytes, granulocytes and dendritic cells. These cells express receptors for the Fc portion of immunoglobulins or complement receptors, or both. Dendritic cells and macrophages are particularly preferred . . . .

The invention is demonstrated by performing the claimed steps, and reporting experimental results aimed at detecting cells that exhibit a specific activity – presentation of antigens. The "phrase antigen-presenting cells" describes the cells in proven functional terms.

Replication-defective Retrovirus

The description of Claims 36-39 mischaracterizes the claimed invention. In particular, the Examiner states that: "Applicants appear to be attempting to find a retrovirus that expresses adequate viral antigen such that a cellular immune response can be obtained, wherein said retrovirus replicates to a low degree without causing disease." The Examiner follows up with a list of information needed to characterize such a virus. The claimed invention, however, does not use a retrovirus of any sort. Retroviruses are made of RNA. The claimed invention uses DNA. Because the claimed invention does not use "a retrovirus that expresses adequate viral antigen such that a cellular immune response can be obtained, wherein said retrovirus replicates to a low degree without causing disease" the Applicants have no duty to describe it.

PEI, PEI derivatives and mixtures thereof

The Applicants note that the language "PEI, PEI derivatives and mixtures thereof" in Claim 23 was admittedly supported by the language of original Claim 8. Further, the patent includes Example 6, "Specifically Targeting DC via Mannose Receptor" where PEI modified with different sugars was chosen to target the mannose receptor....(Col. 14, lines 52-53). Table 1 of that example includes results of various PEI derivatives, including PEI-mannose, -galactose, and –glucose. Col. 15, line1. There is no requirement that an inventor must include examples of every potential permutation of the invention in order to obtain protection. That example, and the presence of the language in the original Claim

demonstrate that the claimed mixtures were reasonably contemplated and within the scope of the invention.

Rejections under 35 USC § 112, 1st para

Claims 23-41

Claims 23-41 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

The claims are drawn to transducing antigen presenting cells (APCs) of the skin by applying a complex to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding a an immunogenic protein and ii) sugar, polyethylenimine (PEI), a PEI derivative, or mixture thereof.

The Examiner admits that the specification describes using the method claimed to induce an immune response in a mammal (pg 20, Example 4), The Examiner adds, without citation, that merely inducing an immune response in a mammal, in and of itself, does not have an enabled use *by law* (emphasis added) because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, the Examiner states that inducing an immune response according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. The Examiner states further that the ordinary artisan reading the claimed invention in view of the specification would only determine that the method claimed was for the purpose of therapy or prophylaxis. The Examiner concludes that applying DNA encoding an immunogenic protein to an animal as claimed is not enabled because the specification does not provide adequate guidance for one of skill to induce a therapeutic or prophylactic immune response using the method claimed.

Further, the Examiner cites the Klatzmann and Sticker references, that are said to have taught retroviral vaccines have been unable to protect against infection (Katzmann, US Patent 6,140,114, Oct. 31, 2000; Stricker et al., Medical Hypotheses, June 1997, Vol. 48, pg 527-9). He cites a further article to show that, generally, a lack of understanding about protective immunity to retroviruses such as HIV, the sequence variability and the rapid replication of retroviruses contribute the ineffectiveness of vaccines against retroviruses (Bangham, Nov. 29, 1997, Lancet, Vol. 350, pg 1617-1621; pg 1617, top of Col. 1).

The Examiner admits that the specification teaches making plasmids encoding replication defective, integrase defective HIV as described in application 08/989,301 (pg 18, line 30-32). The Examiner states that, in application 08/939,301, applicants call such retroviruses "Class 4" viruses which are infectious but replication-defective (pg 15, lines 1-5). The Examiner says that, in application 08/989301, applicants teach that replication defective HIV that does not replicate effectively is inadequate to elicit a protective cellular immune response, or alternatively, that replication defective HIV that does replicate effectively causes disease and sometimes fatal (pg 3, line 17 through pg 4, line 3). The states his view, of the problem, namely that the amount of replication of a retrovirus required to obtain a therapeutic cellular immune response without causing disease was unknown in the art at the time of filing, and that it was also unknown how to make a retrovirus with the adequate amount of replication that would provide an adequate cellular immune response without causing disease. The Examiner states that, without being able to make such a retrovirus, it was unknown how to use such a virus to obtain a therapeutic or prophylactic cellular immune response in a host.

The Examiner states that the specification does not provide adequate guidance regarding how to obtain a therapeutic or prophylactic effect by applying a replication defective retrovirus in an animal as claimed. The Examiner states that the specification does not teach the amount of a cellular immune response that is therapeutic or prophylactic effect against a replication defective retrovirus; the amount of dendritic cells required to obtain adequate antigen presentation is not provided in the specification; the amount of retroviral protein expression required to obtain the desired cellular immune response is not provided in the specification; the amount of replication and infectiousness required to obtain the desired balance between therapy and pathogenicity is not provided in the specification. The Examiner takes the position that, given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine how to make and/or use a replication defective retrovirus to obtain a therapeutic/prophylactic effect without causing disease or death.

The Examiner states that, in addition, it was unpredictable what vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic or prophylactic effect using in vivo or ex vivo gene therapy (Miller 1995, FASEB J., Vol. 9, pg 190-199; pg 198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, Ist ~, pg 65, 1 st T under Conclusion section; Verma, Sept. 1997, Nature, Vol, 389, pg 239-242; see entire article, specifically pg 240, sentence bridging col. 2 and 3; Crystal, 1995, Science, Vol. 270, pg 404410, pg 409; Ross, Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1782, col. 2, 1 st full T; pg 1789, col. 1, 1 5t %

The Examiner states that the specification does not enable applying DNA to the mucosa to target APCs of the skin. It is unclear *how* (emphasis added) application of DNA to the mucosa would result in expression of the protein in the skin. The Examiner says that the specification does not provide the combination of vector, promoter, dosage, level of expression that would result in a therapeutic/prophylactic effect. The Examiner states that, given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine the vector, promoter, cell, dosage, level of expression and route of administration required to obtain a therapeutic or prophylactic effect using the method claimed.

Response – Claims 23-41

The Examiner's analysis relies upon a mistaken interpretation of law that affects the analysis of patentability of the Claims. It is the *claimed* invention that must be analyzed. The claimed invention relates to a method of transducing antigen-presenting cells, and the application is supported by experimental results that demonstrate that this has been achieved. As discussed in the rejection above, that is all that is required by law, but additional evidence is available in the parent patent file showing a therapeutic effect in animals. The Examiner has assembled a set of underlying facts that demonstrate the magnitude of the creative acts that gave rise to this invention.

The Present Invention

The present invention relates to a method of transducing antigen presenting cells the steps comprising selecting a gene delivery complex comprising DNA and a compound

selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, wherein the immunogenic protein is from a lentivirus. The parent patent contains Examples where these steps were performed, and evidence that cells had been transduced. See at least Example 8 of USPN 6,420,176 (Col. 16, lines 2-3) and Example 9 (Col. 16, lines 41-43), where complexes were applied to the skin of mice. Following that step, the balance of the discussion of the experiments reports evidence that transduction of APCs and expression of a marker protein had occurred. For example, at Col. 16, lines 53-55: "These results demonstrate that the complex entered into cells located in the skin, and the cells were able to migrate into the LN [lymph nodes] and express the green fluorescent protein."

Enablement

With respect to the Examiner's requirement re therapeutic/prophylactic effect, the applicants note that there is no such limitation in the claims, and that the Examiner has stated a requirement inconsistent with the legal requirements. These Claims are supported by data showing the use of different DNAs, different compounds, complexes with varying properties, and targeting different receptors. They are supported by both *in vivo* and *in vitro* data in two different animal models. The parent patent contains data showing that genes have been delivered to antigen presenting cells, that the cells then both migrated to the lymph nodes, and expressed protein. *In vitro* CTL responses are reported, along with a report of a clinical result: a CTL response in an animal. In light of all this data, it is not understood how an enablement/utility rejection can be said to lie against this application, unless an examination standard is being applied that is different from those applied to the other technical arts.

Whether patents are allowable in a given particular field of art is not a question of Patent and Trademark Office discretion but of law, and examiners have no discretion to deny patents to inventions meeting the statutory criteria. Animal Legal Defense Fund v. Quigg, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985). The standard for enablement focuses on the person skilled in the art, Radomex, Inc. v. Scopus Corp., 7 USPQ2d 1050 (Fed. Cir. 1988) rather than the general public. For this reason, a specification is not required to teach what is known in the relevant art. Lindeman Maschinenfabrik GmbH v. American Hoist & Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984). Further, when a properly claimed invention meets at least one stated objective, utility under Section 101 is clearly shown. Raytheon v. Roper, 220 USPQ 592 (Fed. Cir. 1983). For an issued patent to be held invalid for lack of utility under Section 101, the challenger must prove that the invention is

totally incapable of achieving a useful result. Brooktree Corp. v. Advanced Micro Devices, Inc., 24 USPQ2d 1403, 1412 (Fed. Cir. 1992). The utility requirement is met where *in vitro* evidence indicates that positive *in vivo* results are likely. Cross v. Iizuka, 224 USPQ 739, 742-43 (Fed. Cir. 19985). Human clinical trials are not required, In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995) and the PTO should not confuse the standard for patentability with the standard for FDA approval id., at 1442.

In this case, the requirement to show a therapeutic/prophylactic response utility objection is clearly inapplicable. The enablement/utility objections find their application in discouraging filings based on hypothetical examples and in cases of fraud, such as In re Oberweger, (baldness cure) 47 USPQ 455, 457 (CCPA 1940), but not more credible cases. See USPN 4,139,619 issued February 13, 1979 for a method of stimulating hair growth by topical application of minoxidil, and note that the text refers to another patent for the method of making the active ingredient in a series of formulations, and for experimental support. The present application contains clear experimental support for the amended Claims, and therefore the present objection must be withdrawn at this time.

With respect to the Klatzmann and Stickler references, the Applicants note those references relate to the retroviral vaccines (not DNA) of others, and demonstrate failure of others. With respect to the Examiner's objection that the specification does not provide adequate guidance regarding how to obtain a therapeutic or prophylactic effect by applying a replication defective retrovirus in an animal "as claimed", the Applicants note that the claimed invention, as discussed above, has been taught, and supported by experimental results.

With respect to the Examiner's objection that the specification does not enable applying DNA to the mucosa to target APCs of the skin, the applicants note that the claims have been amended to avoid that interpretation.

Rejections under 35 USC § 112, 2nd para
Claims 23-41

Claims 23-41 have been rejected under 35 U.S. C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 23 is said to be indefinite because it is said to be unclear whether "mixtures thereof" refers to mixtures of sugars, PEI and PEI derivatives or to mixtures of DNA with sugars, PEI or PEI derivatives.

Claim 23 is said to be indefinite because the preamble requires transducing APCs of the skin, but the body of the claim merely requires applying a complex to the skin/mucosa of an animal. The Examiner comments that it is unclear if transduction of APCs and

expression of the immunogenic protein are clear, positive steps that must occur in the body of the method claimed.

Claim 23 is said to be indefinite because the complex may be applied to the mucosa surface of an animal but the preamble requires transduction of APCs of the skin. The Examiner comments that it is unclear how APCs of the skin can be transduced by application of the complex to the mucosa.

Claim 23 is said to be indefinite because it is unclear if "transduction" is limited to infection with a virus or if it encompasses transfection with plasmid. The specification does not define "transduction"; however, the art sometimes refers to "transduction" as infection with a viral particle. In view of claim 40, which is limited to plasmid, use of the term "transduction" is confusing.

Claim 23 is said to be indefinite because the metes and bounds of what applicants consider "applying" to the skin cannot be determined. The Examiner states that it is unclear if the phrase is limited to putting the complex on the skin or if the phrase encompasses subcutaneous injection which results in delivery of the complex under the skin. It is unclear if intravenous injection is encompassed by the phrase because such an injection does require contact of the complex to the skin when the injection passes through the skin.

Claim 27 is said to be indefinite because it is unclear what applicants consider a mannosylated PEI "derived" from a linear PEI 22kDA. The Examiner says that the metes and bounds of "linear" PEI cannot be determined. The phrase "a linear PEI 22kDN' is confusing because it is unclear if the linear PEI is 22kDA in weight or if PEI 22 kDA refers to some particular type of PEI.

Claim 29 and 30 are said to be indefinite because the phrases "about 3-10:1 molar equivalent polyethylenimine or polyethylenimine derivate amine per DNA phosphate ratio" and "about 5:1 molar equivalent polyethylene mine or polyethylene mine derivate amine per DNA phosphate ratio" are said to be unclear. Page 22, lines 9-16, teaches that at the 5:1 (N:P) ratio, PEI-man-DNA is neutral. The specification states that N and P stand for nitrogen and phosphorus. It is unclear if the phrase is intended to be the limited to the ratio of polyethylenimine derivate amine per DNA phosphate or encompasses the ratio of polyethylene mine derivate amine or polyethylene mine amine per DNA phosphate. The Examiner comments that the phrase "molar equivalent polyethylenimine" seems to be missing a word making the phrase unclear. The metes and bounds of the phrase also cannot be determined because it is unclear what applicants consider "about 5 molar equivalents" of N and P.

Claim 31 is said to be indefinite because it is unclear whether a "glucose solution" encompasses glycosylated PEI (a derivative of PEI as in claim 23) or is limited to glucose in water. The specification teaches PEI may be glycosylated (pg 21, Table 1) or solubilized in glucose (pg 22, line 35). Overall, it is unclear whether the glucose solution is a solution in which the complex of claim 23 is put in or encompasses a complex made up of PEI conjugated with glucose.

Claims 32 and 33 are said to be indefinite because the metes and bounds of the phrase "about 5-10% glucose" and "about 8% glucose" cannot be determined. The Examiner states that the specification does not teach how to determine the units of the 5-10% glucose described on page 22, line 35-36. Thus, the metes and bounds of the claims cannot be determined.

The phrase "activating the antigen presenting cells" in claim 34 is said to be indefinite. According to the Examiner, it is unclear if the phrase is further limiting what happens when the complex is "applied" as in claim 23 or if it is a step that is separate from "applying" the complex that occurs before or after "applying" the complex. It is unclear if "activation" refers to expression of the immunogenic protein in the context of an MHC molecule or to a second, separate step that causes "activation" of the APCs, e.g. applying an interleukin that causes APC activation.

The Examiner comments that the metes and bounds of what applicants consider "activating" APCs by receptor stimulation, toxin activation, or tissue or cell injury in claim

35 cannot be determined, apparently because it is unclear if applicants are attempting to limit how the complex enters the APCs after being applied or if receptor stimulation, toxin activation, or tissue or cell injury causes the APCs to express the immunogenic protein in a particular manner.

It is said that the metes and bounds of proteins "derived" from a reverse transcriptase dependent virus are unclear. It is unclear if the proteins must be isolated from such a virus or must be altered from their natural state (i.e. derived). Deletion of the term "derived" is recommended.

The Examiner takes the position that the metes and bounds of what applicants consider a reverse transcriptase dependent virus in claims 36 and 37 is unclear. It is unclear if the claim is limited to lentiviruses or if the claim encompasses other viruses that are somehow dependent on reverse transcriptase. If the phrase is intended to encompass non - lentiviruses, it cannot be determined how such viruses might be dependent upon reverse transcriptase.

Response – Claims 23-41

The Applicants submit that the present rejections are inapplicable to the Claims as amended.

Claim 23 – "mixtures thereof"

The applicants point out that the claim has been amended as suggested by the Examiner.

Claim 23 – Other steps

The applicants point out that the presently claimed invention is drawn to the steps a person takes to use the invention, as recorded in the experiments in the parent patent. Once the complex is applied to the skin or mucosa, no further positive steps on the part of the user are required. That is, transduction of APCs and expression of immunogenic protein follow without further intervention by the user. See at least Example 8 of USPN 6,420,176 (Col. 16, lines 2-3) and Example 9 (Col. 16, lines 41-43), where complexes were applied to the skin of mice. Following that step, the balance of the discussion of the experiments reports evidence that transduction of APCs and expression of a marker protein had occurred. For example, at Col. 16, lines 53-55: "These results demonstrate that the complex entered into cells located in the skin, and the cells were able to migrate into the LN [lymph nodes] and express the green fluorescent protein."

Claim 23 – transduction/apply

The Claim has been amended along the lines suggested by the Examiner.

Claim 23 – transduction/transfection

The Claim has been amended along the lines suggested by the Examiner.

Claim 23 – applying

The Applicants point out that the claim must be interpreted as a whole. The claimed invention relates to a method of transducing antigen-presenting cells the steps comprising selecting a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, wherein the immunogenic protein is from a lentivirus. In this case, the word "applying" is part of the phrase "applying the complex to the skin or mucosa surfaces." The word apply is defined as "8. to place in contact with; to lay or spread on: to apply paint to a wall; to apply a bandage to a wound." It is therefore clear that the phrase does not apply to injection, which is defined as "to force (a fluid) into a passage, cavity, or tissue: to inject a medicine into the veins" both in the Random House Dictionary of the English Language, 2nd ed. Unabridged. With this explanation, it is believed this objection may be withdrawn at this time.

Claim 27 – derived

The Claim has been amended along the lines suggested by the Examiner.

Claims 29 and 30 – molar equivalent

The Claims have been amended along the lines suggested by the Examiner. It is noted that the Claims are supported by reported actual experiments, in the range of 3:1 to 10:1 N:P; and that the optimal ratio of each of two separate materials has been placed in separate claims, that is, Claim 30 and new Claim 42.

Claim 31 – glucose solution

The Applicants point out that it appears to them the Examiner is asking them to insert a limitation as to a theory into the Claim. The experimental results reported by the Applicants show that, as a practical matter, the complex may be formulated in a glucose solution in at least two ways, namely by forming the PEI-DNA or PEI-mannoseDNA complex and adding it to a glucose solution, or placing DNA in a glucose solution. As a result, it does not matter whether the glucose solution is a solution in which the complex of claim 23 is put in or encompasses a complex made up of PEI conjugated with glucose, because both have been shown to work, and are within the scope of the invention.

Claims 32 and 33 – about/units

In response, the Claims have been amended as suggested by the Examiner.

Claims 34 and 35 – activating

In response, the Claims have been amended as suggested by the Examiner.

Claims – Derived

In response, the Claims have been amended as suggested by the Examiner.

Claims 36 and 37 – Reverse Transcriptase dependent

In response, the Claims have been amended as suggested by the Examiner.

Claim Rejections - 35 USC § 102

Claims 23-35, 40 and 41

Claims 23-35, 40 and 41 have been rejected under 35 U,S,C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) The parent application 60/058,933, does not describe complexing DNA with a compound selected from the group consisting of sugars, PEI, PEI derivatives, or mixtures thereof (claim 23). Therefore, the claimed invention does not get priorty back to 9-15-97. Parent application 09/153,198 does not describe complexing DNA with a glucose solution (claim 31). Therefore, the claims in general have priority to 9-15-98, except for claims 31-33 relating to a "glucose solution," which have an effective filing date of 2-21-02.

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1 –19)

Claims 25-27 are included because they are not limited to a compound that is mannosylated PEI or PEI "derived from a linear PEI 22 kbA;" claims 25-27 encompass glucose as in parent claim 24.

Claims 28-30 are included because Behr taught that between 5-20 equivalents of PEI amines, are used relative to DNA phosphates (col. 8, lines 15-19), specifically 9 equivalents (col. 12, line 58). The instant specification teaches that such ratios cause the complex to be electrostatically neutral (I bridging pg 21-22).

Claim 33 is included because 5% is "about 8% as claimed.

Claims 34, 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Response–Claims 23-35, 40 and 41

The applicants respectfully submit that the present rejection is inapplicable to the amended Claims, at least because they incorporate all the limitations of Claim 36, in the form preferred by the Examiner, which was not subject to the present rejection. Claim 36 originally used the term "reverse transcriptase dependent virus" and the Examiner has objected that the term should be "lentivirus."

Priority

The applicants note that the Examiner has admitted that the quoted language with respect to Claim 23 was found in original Claim 8. That language unquestionably has the priority of the original file date of the parent patent. The claim language has been amended as suggested by the Examiner. The "glucose solution" language is found in the parent patent at Col. 15, line 67, and is entitled to the original file date of the parent.

Claim Rejections – 35 USC § 103

Claims 23-38, 40 and 41

Claims 23-38, 40 and 41 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) in view of Adachi (J. Virol., 1986, Vol, 59, pages 284-291) and Owada (Microbiol. Immunol. Feb. 1998, Vol. 242, No. 2, pg 97-107).

The Examiner states that the parent application does not describe a "glucose solution" (claim 31), and that therefore, the effective filing date of claims 31-33 is the filing date of parent application 09/153,198, which is 9-15-98.

Behr is said to have taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). The Examiner states without citation that Luciferase, which is a common marker gene, is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr is said to have taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1 -19). The Examiner admits that Behr did not teach the immunogenic protein was derived from a reverse transcriptase dependent virus. However, Adachi taught a plasmid encoding replication-defective HIV used for transfecting a wide array of eukaryotic cells (pg 284, col. 2, 8 lines from the bottom; pg 285, col. 1, Table 1; pg 289, Table 2).

Thus, it would have been obvious for one of ordinary skill in the art at the time the invention was made to administer a complex of a plasmid encoding an immunogenic protein and PEI in a glucose solution to the skin/mucosa of an animal to express the protein in cells of the animal as taught by Behr wherein the plasmid encoded HIV proteins as taught by Adachi, One of ordinary skill in the art would have been motivated to use PEI to administer the plasmid of Adachi because PEI increased transfection as compared to DNA alone (Behr, col. 8, lines 13-19; col. 13, lines 6-10). One of ordinary skill in the art would have been motivated to replace the plasmid encoding luciferase with the plasmid encoding H IV proteins to determine whether an immune response against the HIV antigens would occur in vivo. One of ordinary skill in the art at the time the invention was made would have been motivated to use PEI to deliver DNA encoding HIV proteins because it was well known in the art at the time of filing that PEI could be used to deliver DNA encoding HIV proteins to cells (Owada, see pg 98, "Cells and Virus", "Compounds"),

Thus, the Examiner states that the Applicants' claimed invention as a whole is prima facie obvious in the absence of evidence to the contrary.

Response–Claims 23-38, 40 and 41

The applicants respectfully submit that the present rejection is inapplicable to the amended Claims, at least because they incorporate all the limitations of Claim 36, which was not subject to the previous rejection. Neither the Adachi nor the Orwada references fill in the gaps in the base reference. The Adachi reference reports the construction of an infectious molecular clone of HIV that was tested for the ability to produce infectious virus particles in a wide variety of cell lines. The Orwada reference reports the construction of a defective integrase gene. Neither discloses or discusses the claimed method, or presents any rationale for using the claimed method over any other.

Priority

Support for the claim language relating to "glucose solution" is found in the text of the parent patent, USPN 6,420,176, at least at Col. 15, line 67, and is entitled to at least the original patent's file date of Sept. 15, 1998. The inventors explained in Example 10, Col. 17, lines 17-19 that "Experimental results depicted in Table 2 provided evidence that a sugar-DNA complex, in the absence of PEI-man, can transduce Langerhans cells *in vivo*." Table 2 reports results obtained in an experiment where the complexes were formulated in glucose solution and the transcutaneous and subcutaneous modes of delivery were compared. In Example 10, it is explained that surprisingly good results were obtained in one of the transcutaneous controls, where plasmid DNA without either PEI or PEI-mannose, was formulated in glucose solution. The inventors concluded that "It shows that sugars ... can also complex DNA and deliver the DNA to the Langerhans cells via the mannose receptor."

Rejection under 35 USC §103

The Applicants point out that the teachings of the references are by no means so clear and precise as they appear in the Examiner's summary, because the Examiner, guided only by the teachings of the Applicants, has used snippets and short quotes selected from the base reference to piece together the rejection. This is a classic case of hindsight reconstruction of a claimed invention based only on guidance from Applicant's disclosure. The Federal Circuit has required that, in order to avoid hindsight reconstruction, the Examiner must point to guidance, or connecting teaching outside that provided by the Applicants to suggest that the desirability of the claimed combination and the expectation that that specific combination will be successful. The Examiner does not cite any guidance to be found in either the base reference or the additional references, that would lead one of

ordinary skill in the art to have a reasonable expectation that the claimed invention would work, or that the advantages of the claimed invention could be obtained.

Instead, the Examiner points to a motivation on the part of a hypothetical researcher to do an experiment. That, at best, and assuming *arguendo* the teachings of the references are as clear as stated, would only mean that it would have been obvious to try the experiment. Obvious to try is not the standard of patentability. Rather, both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) MPEP 2143.01.

The Claimed Invention

A method of transfecting antigen-presenting cells, the steps comprising selecting a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, wherein the immunogenic protein is from a lentivirus. There is no teaching or suggestion anywhere in the prior art that the presently claimed method would work, or that its advantages could be obtained.

The Behr Reference

The Behr reference relates to the use of PEI as an adjuvant for gene therapy, preferably in conjunction with plasmid DNA, although a wide variety of other materials are disclosed as well. The reference states that PEI can be used in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), in a wide variety of configurations, including using a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57), for a wide variety of purposes (for example, the production of therapeutic products including enzymes, blood derivatives, hormones, lymphokines,...growth factors, neurotransmitters...synthetic enzymes, etc,, -- a list that includes thousands of items. See Col. 3, lines 29-44. Antigenic peptides are also listed at Col. 3, line 57-67, as well as antisense genes (Col. 3, line 45), sequences (Col. 4, line 1, and upstream signals to control therapeutic genes (Col. 4, lines 25-29) and that it can be used in formulations with a view to topic, cutaneous, oral, rectal, vaginal, parenteral, intranasal,

intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like (Col. 6, lines 1-4). Both direct injection and topical administration are said to be preferred (Col. 6, lines 5-9), but only direct injection is shown in any experiments, and there is no disclosure of how to accomplish gene delivery by means of topical administration. The patent does not disclose how to target antigen presenting cells of the skin, or formulations that can be used for needleless, *in vivo* delivery of genes into any cells, much less antigen presenting cells, or any *in vivo* method of delivery except injection.

This reference has disclosure consistent with that for a new material or a new use for a material with potentially wide application in a given field. What is beyond the scope of this reference is specific instruction as to how to realize the full potential of the material, that is, how to obtain the results that are potentially available from it, in areas that were not of direct interest to the inventors of the reference at the time.

The Adachi Reference

The Adachi reference reports the construction of an infectious molecular clone of HIV that was tested *in vitro* for the ability to produce infectious virus particles in a wide variety of cell lines. The disclosed method of transfection was calcium phosphate precipitation. It adds nothing to the Behr reference.

Owada

The Owada reference, "Enhancement of Human Immunodeficiency Virus Type 1 (HIV-1) Infection via Increased Membrane Fluidity by a Cationic Polymer" Microbiol. Immunol. 42(2), 97-107, 1998, reports that PEI was screened as a drug *in vitro* for antiviral activity, and found to have some, but it was also shown to increase the rate of HIV-1 infection of CD4 cells by facilitating virus entry into the host cells. This reference does not address the use of PEI as a method of delivering genes at all, much less the claimed method of delivering genes into antigen presenting cells.

Analysis

Neither the base reference nor the secondary references supply the specific information needed to make the claimed invention or show how the advantages of the claimed invention could be obtained. The combination does not meet the established criteria for rendering the claimed invention obvious. In particular, there is no linking teaching or guidance that would lead one of ordinary skill in the art to select the bits and pieces of the claimed invention from the voluminous options presented in the base reference. The

secondary and tertiary references do not fill the gaps in the base reference. This rejection should be withdrawn at this time.

Claim Rejections – 35 USC § 103

Claims 23-41

Claims 23-41 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) in view of Adachi (J. Virol., 1986, Vol.. 59, pages 284-291) and Owada (Microbiol. Immunol. Feb. 1998, Vol. 242, No. 2, pg 97 107) as applied to claims 23-38, 40 and 41, further in view of Holler (US Patent 5,908,923).

The Examiner contends that the parent application does not describe a "glucose solution" (claim 31). Therefore, the effective filing date of claims 31-33 is the filing date of parent application 09/153,198, which is 9-15-98.

The Examiner states that the combined teachings of Behr, Adachi and Owada taught a complex comprising i)- PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding an HIV protein operatively linked to a promoter suspended in 5% glucose (see 103 rejection above), but admits that the combined teachings of Behr, Adachi and Owada did not teach the immunogenic protein was derived from an integrase defective HIV virus.

However, the Examiner says that the Holler reference taught a plasmid encoding replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54).

Thus, the Examiner concludes that it would have been obvious for one of ordinary skill in the art at the time the invention was made to administer a complex of a plasmid encoding an HIV protein and PEI in a glucose solution to the skin/mucosa of an animal to express the protein in cells of the animal as taught by the combined teachings of Behr, Adachi and Owada wherein the plasmid encoding HIV proteins was integrase defective as taught by Holler, because one of ordinary skill in the art would have been motivated to make the HIV integrase defective to prevent causing disease in the animal.

Thus, Applicants' claimed invention as a whole is prima facie obvious in the absence of evidence to the contrary.

Claims 23-41 – Response

Priority

Support for the claim language relating to "glucose solution" is found in the text of the parent patent, USPN 6,420,176, at Example 10, Col. 17, lines 17-19: "Experimental results depicted in Table 2 provided evidence that a sugar-DNA complex, in the absence of PEI-man, can transduce Langerhans cells *in vivo*." Table 2 reports results obtained in an experiment where the complexes were formulated in glucose solution and the transcutaneous and subcutaneous modes of delivery were compared. In Example 10, it is explained that surprisingly good results were obtained in one of the controls, where plasmid DNA without either PEI or PEI-mannose, was formulated in glucose solution. The inventors concluded that "It shows that sugars ... can also complex DNA and deliver the DNA to the Langerhans cells via the mannose receptor."

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The Applicants point out that the teachings of the references are by no means so clear and precise as they appear in the Examiner's summary, because the Examiner, guided only by the teachings of the Applicants, has used snippets and short quotes selected from the base reference to piece together the rejection. This is a classic case of hindsight reconstruction of a claimed invention based only on the Applicant's disclosure. The Federal Circuit has required that, in order to avoid hindsight reconstruction, the Examiner must point to guidance, or connecting teaching outside that provided by the Applicants to suggest that the claimed combination should be made. The Examiner does not cite any guidance to be found in either the base reference or the additional references, that would lead one of ordinary skill in the art to have a reasonable expectation that the claimed invention would work, or that the advantages of the claimed invention could be obtained.

Instead, the Examiner points to a motivation on the part of a hypothetical researcher to do an experiment. That, at best, and assuming *arguendo* the teachings of the references are as clear as stated, would only mean that it would have been obvious to try the experiment. Obvious to try is not the standard of patentability. Rather, both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) MPEP 2143.01.

The Claimed Invention

A method of transfecting antigen-presenting cells, the steps comprising selecting a gene delivery complex comprising DNA and a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives and mixtures thereof, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, wherein the immunogenic protein is from a lentivirus. There is no teaching or suggestion anywhere in the prior art that the presently claimed method would work, or that its advantages could be obtained.

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This reference has disclosure consistent with that for a new material or a new use for a material with potentially wide application in a given field. What is beyond the scope of this reference is specific instruction as to how to realize the full potential of the material, that is, how to obtain the results that are potentially available from it in areas that were not of direct interest to the inventors at the time.

The Adachi Reference

The Adachi reference reports the construction of an infectious molecular clone of HIV that was tested for the ability to produce infectious virus particles in a wide variety of cell lines. It adds nothing to the Behr reference.

Owada

The Owada reference, "Enhancement of Human Immunodeficiency Virus Type 1 (HIV-1) Infection via Increased Membrane Fluidity by a Cationic Polymer" Microbiol. Immunol. 42(2), 97-107, 1998, reports that PEI was screened as a drug *in vitro* for antiviral activity, and found to have some, but it was also shown to increase the rate of HIV-1

infection of CD4 cells by facilitating virus entry into the host cells. This reference does not address the use of PEI as a method of delivering genes at all, much less the claimed method of delivering genes into antigen presenting cells.

USPN 5,908,923 to Holler, et al.

The Holler reference discloses and claims a sequence listing for a specific transdominant negative integrase gene which is said to be capable of making at least one cell resistant to a retroviral infection. The Examiner states that the reference teaches a plasmid encoding a replication-defective HIV that was integrase defective for use *in vivo* based on the disclosure from Col. 4, lines 51-54. The disclosure is quoted in full below.

> Thus, in a tenth aspect, the present invention is directed to a method of treating AIDS in a patient comprising administering to said patient a therapeutically effective amount of a transdominant negative integrase gene. Col. 4, lines 51-54.

The applicants point out that this disclosure simply amounts to a suggestion that the gene is useable. It says nothing about the claimed method. Indeed, this 1994 reference would appear to recommend that the gene can be successfully delivered by any and all methods. However, the parent patent of the present application, USPN 6,420,176, discloses that an article published several years later reported only "low efficient" *in vitro* methods were known at the time, (cites to Arthur, J. F. et al., Cancer Gene Therapy 4:1 17-21, 1997 and Song, E. S., et al., PNAS USA 94:5, 1943-8, 1997); and that neither they nor the known *in vivo* methods had been shown to effectively deliver genes to antigen presenting cells, much less delivery of genes through the skin into the Langerhans cells. (USPN 6,420,176 Col. 3, line 60-Col. 4, line 12). Thus, this reference adds nothing to the cited combination.

Analysis

In order for an obviousness rejection to stand, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art. This standard is not met by broad statements that one "can" use broad arrays of materials and techniques. Neither the base reference nor the secondary and tertiary references supply the specific information needed to select the elements of the claimed invention or show why the claimed invention would be expected to work. Further, the motivation cited by the Examiner is, at best, motivation to do an experiment. Assuming that motivation could be shown, it would only render the experiment obvious-to-try. Again, obvious-to-try is not the standard of patentability. This rejection should be withdrawn at this time.

Double Patenting

Claims 23-41 of this application are said to conflict with the claims of Application No. 08/989,301. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claims 23-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 08/989,301. Although the conflicting claims are not identical, they are not patentably distinct from each other because they require administering DNA encoding retroviral proteins to the skin/mucosa/dendritic cells of an animal.

This is a provisional obvious ness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting – Response

The applicant notes that the cited application has issued as USPN 6,130,089, which is related to materials and methods to enhance gene transfer, namely the increase of dNTP concentration to make cells more susceptible to a delivery vehicle. This is a promising *in vitro* technique that is not being used in the current invention.

Conclusion

For all the above reasons and amendments, it is believed that the Examiner's concerns have been fairly met. Favorable consideration is solicited.

Respectfully Submitted,

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